

Application no.: 08/786,988

Docket no.: SEQ-2001-UT2

REMARKS

Of claims 108-146 pending, claims 135, 141, 142 and 143 are amended herein. The claim amendments are directed to commercial embodiments, and the amendments add no prohibited new matter as they find basis in the specification. Entry of the new claims therefore is proper.

Information Disclosure Statement

The Applicants thank the Examiner for reviewing and initialing the PTO-1449 form submitted with the supplemental information disclosure statement (IDS) filed on 08 December 2004. Applicants wish to note that this supplemental IDS included incorrect information. The statement pursuant to 37 C.F.R. §1.97(d)(1) and (e)(1) in the second paragraph of the supplemental IDS was not pertinent to documents cited in the attached PTO-1449 form. Also, the fee of \$180.00 referenced in the third paragraph of the supplemental IDS was not paid to the Office.

This information was inadvertently included without deceptive intent and has no ramification with respect to the initialed PTO-1449 form. It is respectfully submitted that the statement under 37 C.F.R. §1.97(d)(1) and (e)(1) and the \$180.00 fee were not required since the supplemental IDS was filed pursuant to 37 C.F.R. §1.97(b)(4), in conjunction with a Request for Continued Examination (RCE), and before the mailing of a first Office action in response to the RCE. Thus, the Examiner correctly initialed the citations on the PTO-1449 form pursuant to 37 C.F.R. §1.97(b)(4), and therefore the incorrect statements in the supplemental IDS had no effect.

Enablement Rejection

The Office rejected claims 140-143 for alleged lack of enablement under 35 U.S.C. § 112, first paragraph. The Office reasoned that "[t]here is no way for a routineer in the art to obtain reproducible MALDI spectra if only one spot contains the analyte." Amended claim 135, from which claim 141 depends, is directed to depositing analyte on "spots" of the array. Claims 141 and 143 are directed to obtaining MALDI mass spectra from "spots" of the array. As claim 142 depends from claim 141 and includes its limitations, amended

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claims 141-143 clearly refer to obtaining reproducible MALDI spectra from multiple spots. It is therefore respectfully submitted that the rejection is moot with respect to these claims.

It is not understood why the rejection is applied to claim 140, as this claim specifies the amount of matrix is reproducible from spot to spot. Claim 108 from which it depends specifies matrix is deposited "at a plurality of discrete locations on the surface of a substrate." Thus, it is respectfully submitted that the rejection is inapplicable to claim 140, and clarification respectfully is requested if the rejection is maintained.

Indefiniteness Rejection

The Office rejected claims 141-143 for alleged indefiniteness under 35 U.S.C. § 112, second paragraph. The stated reason for the rejection was that there was no active method step in the rejected claims. The Applicants thank the Examiner for suggesting language for an active method step that would overcome the rejection. Claims 141 and 143 have been amended to recite an active method step. Because claim 142 depends for claim 141 and includes its limitations, it is respectfully submitted that the rejection is moot.

Obviousness Rejection: Combination of Vestal, Vorm and Hayes

Claims 108-118, 120-123, 125, 132-141 and 143-146 were rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Vestal in view of Vorm *et al.* and Hayes *et al.* The Office states Vestal teaches an apparatus for automated MALDI mass spectrometric (MS) analysis for a plurality of DNA samples combined with matrix. The Office acknowledges that Vestal does not teach depositing MALDI matrix without an analyte or allowing a spot of matrix to dry in the absence of an analyte. The Office interprets Vorm as teaching methods for depositing microliter volumes of matrix on a MALDI MS probe tip. While acknowledging that Vestal and Vorm do not teach depositing 0.2 to 20 nanoliter volumes, the Office concludes that it would have been obvious to modify Vestal's method of MALDI MS analysis with Vorm's method of depositing MALDI matrix, and that Hayes provides a teaching of dispensing the claimed volumes.

Claimed subject matter is *prima facie* obvious only when the cited document or combination of documents teaches or suggests all of the claimed elements, the person of ordinary skill in the art was motivated to modify the document(s) as suggested in the Office action, and there was a reasonable expectation of success. See MPEP 2142, et seq.

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This rejection respectfully is traversed in part because Vorm teaches away from depositing nanoliter volumes of matrix on a substrate as claimed. Independent claim 108 specifies that a 0.2 to 20 nanoliter volume of matrix is deposited at multiple locations on a substrate. Dependent claims 144 and 145 specify that the matrix spot is defined by 800 by 800 micrometers or less or 450 by 450 micrometers or less, whereby the spots are less than 1 mm in diameter.

Instead, Vorm applies larger volumes of matrix to a probe tip than specified in the claims. Vorm applies 0.5, 0.2 and one microliter volumes of matrix to a probe tip rather than the 0.2 to 20 nanoliter volumes claimed. Vorm states that applying a one microliter volume of matrix results in a spot size about 10 mm in diameter, which is far greater than the diameter resulting from the dimensions specified in claims 144 and 145. Vorm notes on page 3283, left column, that probe tips having a 1.3 mm diameter were utilized, which also is greater than the diameter resulting from the parameters in claims 144 and 145. Vorm further states on page 3285, left column:

The surface area of crystals should be very large in the current method (emphasis added).

Vorm states the surface area of the crystals should be "very large" so that only the outer surface of the crystal is redissolved by protein analyte (page 3285, left column). In keeping with this teaching, the artisan was discouraged from reducing the amount of matrix deposited on a substrate to the 0.2 to 20 nanoliter volume claimed as crystals with smaller surface areas may result. The 0.5 microliter and 0.3 microliter analyte volumes applied by Vorm would have saturated the 0.2 to 20 nanoliter spots as claimed, rather than redissolving the matrix surface, since such analyte solutions are more than 10 times to 100 times greater in volume than the matrix volume deposited (e.g., Figure 2 and Figure 3 legends).

Thus, Vorm suggests the surface area of the matrix crystals should be very large and teaches away from depositing the 0.2 to 20 nanoliter volume of matrix to a substrate as claimed. As a result, there was no motivation to reduce the volume of matrix to that claimed, and the artisan had no reasonable expectation that reducing the matrix volume deposited on a substrate would successfully lead to reproducible MALDI mass spectra.

The motivation to reduce the matrix volume lacking in Vorm and Vestal also is lacking in Hayes. The disclosure in Hayes does not address mass spectrometry or MALDI analysis, fails to

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mention "matrix," and is instead directed to methods for constructing diagnostic arrays having large numbers of probes. Hayes discussed an apparatus having multiple reservoirs for depositing different components on a substrate, not depositing matrix on substrates for MALDI MS. Hayes is silent with regard to providing nanoliter volumes of matrix for enhanced spot to spot reproducibility of MALDI mass spectra. A general discussion of repeatably depositing small volumes of probes on a substrate provides no motivation to deposit small volumes of matrix on a substrate for MALDI MS analysis. Hayes focused on increasing probe density on chips, and did not suggest the desirability of reducing the volume of matrix deposited for MALDI MS. The artisan therefore had no reasonable expectation that reducing the volume of matrix on a substrate would successfully lead to reproducible MALDI mass spectra in view of Hayes. Hayes therefore provided no motivation to the artisan for depositing a 0.2 to 20 nanoliter volume of matrix as claimed when preparing a substrate for MALDI MS analysis.

Vorm also failed to teach or suggest depositing matrix in an array of spots. Vorm dispensed matrix in one spot on a probe tip. As none of the other documents in the cited combination teach or suggest depositing matrix, without analyte, in an array of spots, the claimed subject matter is not obvious over the combination of documents.

Thus, there was no motivation to reduce the volume of matrix deposited to 0.2 to 20 nanoliters, or deposit matrix in an array of spots, provided by the combination of Vestal, Vorm and Hayes. Withdrawal of the rejection respectfully is requested.

Obviousness Rejection: Combination of Nicola and Hayes

Claims 108-118, 120-123, 125, 132-141 and 143-146 were rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Nicola *et al.* in view of Hayes *et al.* The Office states Nicola teaches depositing microliter volumes of matrix on a MALDI MS substrate and applying protein analyte. The Office acknowledges that Nicola does not teach depositing drops of matrix in 0.2 to 20 nanoliter volumes or performing MALDI MS for nucleic acids. The Office quotes column 2, lines 49-55 of Hayes, stating that it would have been obvious to modify Nicola's MALDI MS analysis by using Hayes' method of depositing very small droplets (less than 1 nL) of the matrix material. The stated motivation to combine the documents is that Hayes teaches depositing smaller volumes increases reproducibility of the spots and MALDI MS was a well recognized method for analyzing DNA.

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The rejection respectfully is traversed in part because Nicola teaches away from depositing nanoliter volumes of matrix on a substrate. As noted above, independent claim 108 specifies that a 0.2 to 20 nanoliter volume of matrix is deposited at multiple locations on a substrate. Dependent claims 144 and 145 specify that the matrix spot is defined by 800 by 800 micrometers or less or 450 by 450 micrometers or less, which equate to areas of 0.64 mm^2 or less or 0.20 mm^2 or less, respectively.

Instead, Nicola teaches that the artisan should apply much larger amounts of matrix as compared to the amount of matrix claimed. Nicola spots about 2.5 to 10 microliter volumes of matrix, rather than the 0.20 to 20 nanoliter volumes claimed (page 1166, left column). Further, Nicola states that the spot sizes ranged from 25 to 100 mm^2 , sizes far greater than the 0.64 mm^2 and 0.20 mm^2 areas of claims 144 and 145 (page 1166, left column). Nicola also specified that these larger amounts of matrix:

resulted in greater crystal thickness compared to previously published results **which we consider essential for improvement in signal reproducibility** (as previously reported, ¹³ much less matrix was used for the matrix crystal layer resulting in a much thinner layer).

Page 1166, left column, "Fast-evaporation sample preparation" section (emphasis added). The previous report in reference 13 is the Vorm document addressed above.

Thus, Nicola teaches that greater amounts of matrix than that claimed should be deposited, which are even greater than the amounts taught in Vorm, and that smaller amounts of matrix should not be used. Stated another way, because Nicola considers the greater thickness afforded by microliter deposition of matrix essential for improved signal reproducibility, it taught away from depositing the smaller volumes of matrix claimed. Accordingly, a person of ordinary skill in the art would not have attempted to reduce the microliter volumes of matrix utilized in Nicola to the 0.2 to 20 nanoliter volumes claimed because Nicola taught away from such a modification. Also, the artisan had no reasonable expectation that reducing the volume of matrix deposited on a chip would successfully lead to reproducible MALDI mass spectra.

Thus, there was no motivation to reduce the microliter volume of matrix deposited in Nicola to the claimed amounts as Nicola taught away from such a reduction. Hayes also provided no

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motivation to reduce the volume of matrix deposited in Nicola, as described in greater detail above. Accordingly, withdrawal of the rejection respectfully is requested.

Obviousness Rejection: Combination of Documents Discussed Above with Hancock

Claims 119, 124 and 126-131 were rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Nicola *et al.* in view of Hayes *et al.* or Vestal in view of Vorm *et al.* and Hayes *et al.*, further in view of Hancock. The Office stated that Hancock disclosed the substrate materials specified by the rejected claims. Claims 119, 124 and 126-131 directly or indirectly depend from claim 108 and include its limitations. The rejection therefore respectfully is traversed as Hancock fails to remedy the deficiencies described above. Hancock fails to provide any motivation for reducing the volume of matrix deposited on a substrate to the volumes claimed. Accordingly, withdrawal of the rejection respectfully is requested.

Thus, it is respectfully submitted that the subject matter of claims 108-146 is **not** *prima facie* obvious over the documents or combinations of documents cited in the Office action.

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CONCLUSIONS

Applicants respectfully submit that the pending claims are in condition for allowance, and they earnestly solicit an early notice to such effect. That said, should any issues or questions remain, the Examiner is encouraged to telephone the undersigned at (858) 623-9470 so that they may be promptly resolved.

In the unlikely event the transmittal letter is separated from this document and the Office determines that an extension and/or other relief is required, Applicants petition for any required relief, including extensions of time, and request that an Office representative telephone the undersigned for immediate payment of any fee due.

Respectfully submitted,

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